Oral, Once-daily, Paltusotine (Non-peptide Selective Somatostatin Receptor Subtype 2 Agonist) Therapy in Patients With Acromegaly Is Associated With Long-term Biochemical and Symptom Control and Is Preferred Over Injectable Somatostatin-receptor Ligands

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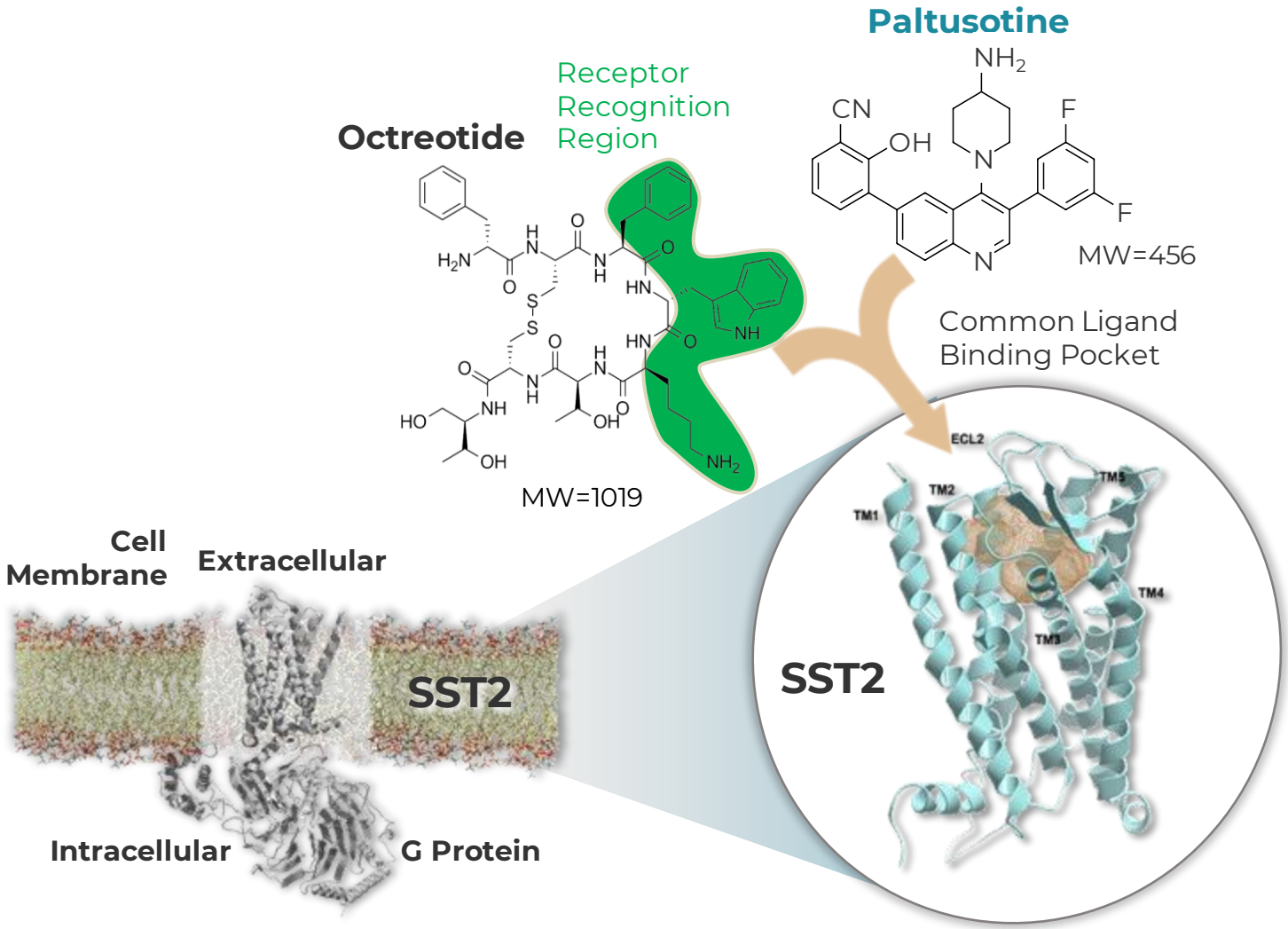
Paltusotine is an investigational compound in development for the treatment of acromegaly.

Presenting Author Disclosures

- ✓ Principal research investigator - clinical trials: Crinetics and Recordati Rare Diseases
- ✓ Speaker fee: Novo Nordisk, Ipsen, Recordati Rare Diseases
- ✓ Advisory board member: Crinetics, Recordati Rare Diseases, Ipsen, Novo Nordisk
- ✓ Funding for this study is provided by Crinetics Pharmaceuticals, Inc.

Paltusotine Is A Once Daily, Oral, Selectively-Targeted Somatostatin Receptor Type 2 (SST2) Agonist



In Vitro Selectivity at All Five Somatostatin Receptor Subtypes for Paltusotine and Somatostatin

Agonist	Human EC_{50} (nM)				
	SST1	SST2	SST3	SST4	SST5
Paltusotine[1]	>10000	0.25	3300	1100	>10000
Native SS14[2]	0.83	0.14	0.17	0.21	0.065

Oral solution bioavailability[3]*	**70%**
Observed half life[3]	**~30 hours**

*Paltusotine administered was as an oral solution in study CRN00808-06. Oral bioavailability for spray-dried dispersion tablet is ~45% administered fasted.

1. Zhao J, Wang S, Markison S, et al. *ACS Med Chem Lett*. 2022 Dec 10;14(1):66-74. doi: 10.1021/acsmedchemlett.2c00431. PMID: 36655128; PMCID: PMC9841592.
2. Juliana CA, Chai J, Arroyo P, et al. *J Biol Chem*. 2023 May 11:104816. doi: 10.1016/j.jbc.2023.104816. Epub ahead of print. PMID: 37178920.
3. Madan A, Luo R, Ferrara-Cook C, et al. *Endocrine Abstracts* 2020 (Vol. 70) (www.endocrine-abstracts.org/ea/0070/ea0070aep627).

Subjects from Parent Trials Enrolled into ACROBAT Advance

Primary Population

Subjects treated with somatostatin receptor ligands (SRLs) who completed either the Edge or Evolve studies

Evolve

Baseline IGF-1 ≤1x ULN

9 Weeks Paltusotine Treatment → 4 Weeks Randomized Withdraw → 4 Weeks Washout → n=11

Edge

Baseline IGF-1 >1x ULN or ≤ 1x with intensive treatment[1]

13 weeks Paltusotine Treatment → 4 Weeks Washout → n=32

88%
of Eligible Subjects Enrolled

ACROBAT Advance

Open Label Extension Study

Paltusotine Treatment
Subjects started on 10 mg and titrated to 40 mg based on IGF-1. Adjunctive treatment as needed to achieve target IGF-1 (expected for Edge Subset)

Start — Year 2 Interim Analysis — Year 4

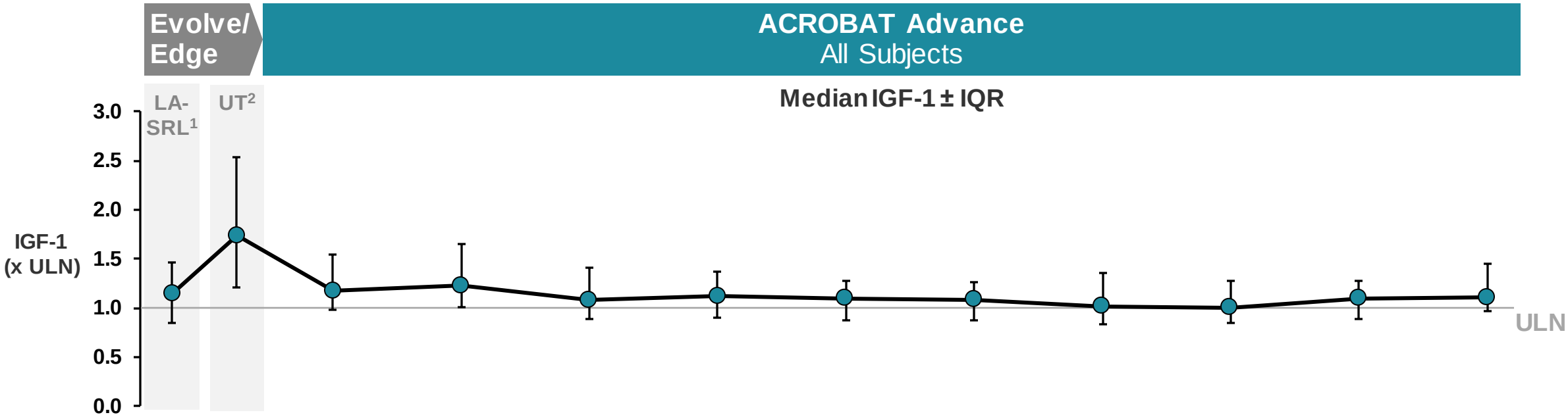
1. SRL + cabergoline, pasireotide monotherapy, or SRL + pegvisomant.

Baseline Characteristics in ACROBAT Advance

	All Subjects N=43
Age, Mean (SD)	53.0 (11.61)
Sex, Female, n (%)	24 (55.8)
Months since diagnosis, Mean (SD)	129.4 (78.4)
Prior pituitary surgery, n (%)	37 (86.0)
Pre-trial medical treatment[1]	
Lanreotide, n - 60/90/120 mg/month	1/2/14
Octreotide, n - 20/30/40 mg/month	3/17/3
Pasireotide (Edge), n - 40/60 mg/month	1/1
SRL + Cabergoline (Edge), n	10
Pegvisomant (Edge), n - 20 mg/week	1

1. Pre-trial is defined as prior to parent trial for direct rollovers and prior to ACROBAT Advance for delayed rollovers.

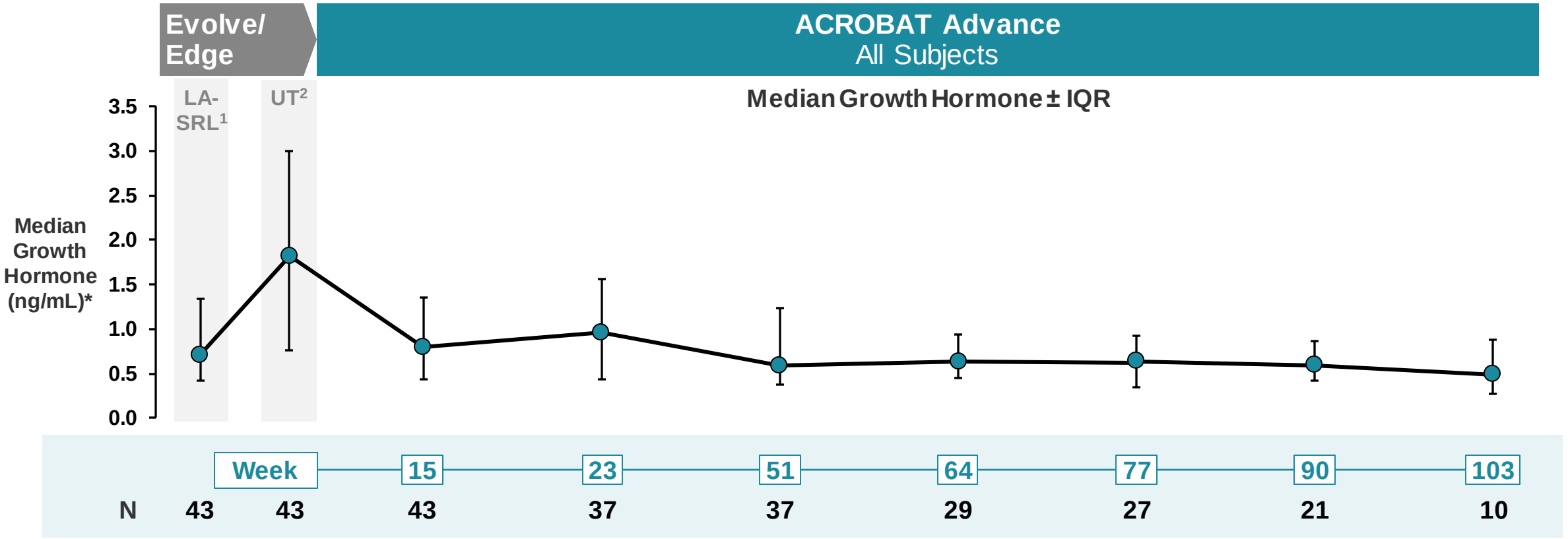
IGF-1 Levels Maintained at Injected LA-SRL Baseline Levels After Switching to Paltusotine



Week		3	15	31	39	47	51	64	77	90	103
N	43 43	43	42	39	37	38	37	31	27	21	10
Cumulative Discons.		0	0	2	3	3	3	5	6	6	6
Med. Paltusotine Dose (mg)		10	30	40	40	40	40	40	40	40	40
Cabergoline Use* (n)		0	1	4	8	14	15	13	11	10	5
Pegvisomant (n)		0	0	0	0	0	0	0	1	1	0

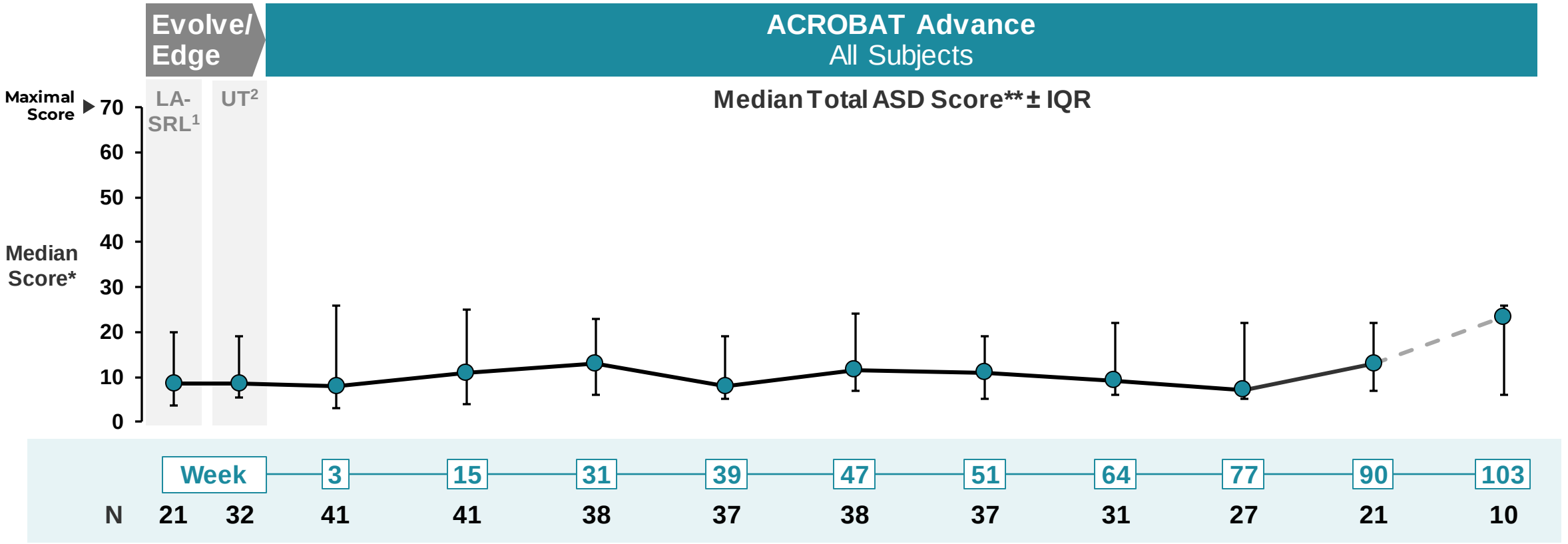
1. Baseline (screening) from Evolve/Edge studies while on injected SRL therapy. 2. End of 4-week wash-out from paltusotine at end of Evolve/Edge studies.
* UT: Untreated

Growth Hormone Levels Remained Stable Over Time



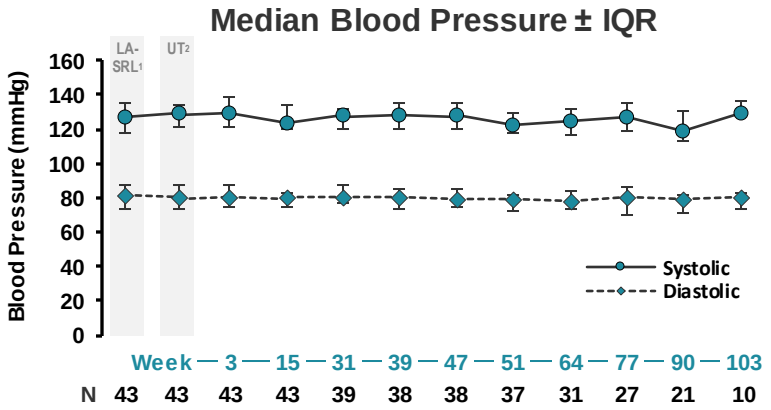
1. Baseline (screening) from Evolve/Edge studies while on injected SRL therapy. 2. End of 4-week wash-out from paltusotine at end of Evolve/Edge studies.
* Single measurement. UT: Untreated.

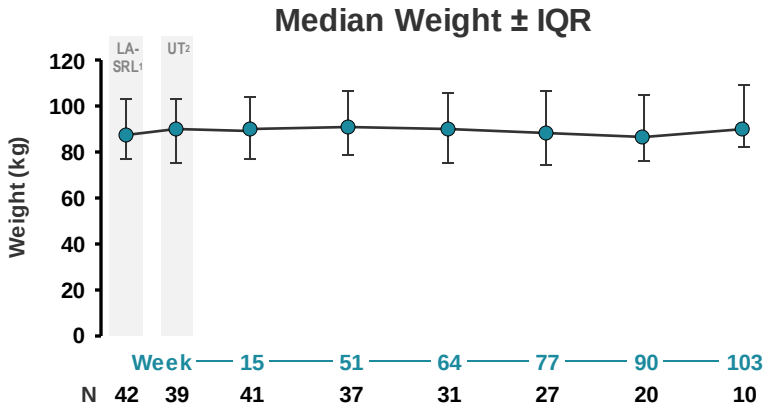
Acromegaly Symptom Diary (ASD) Scores Indicated Low Symptom Burden and Were Stably Controlled

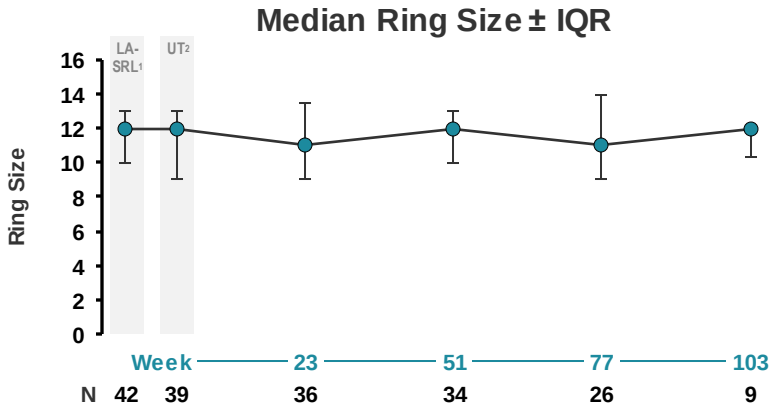


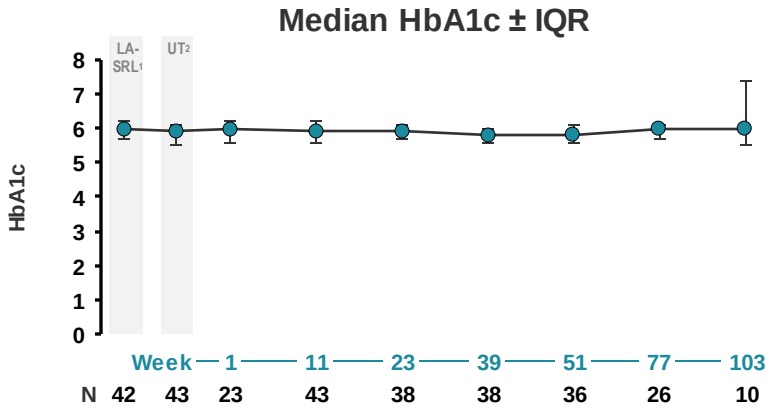
1. Baseline (screening) from Evolve/Edge studies while on injected SRL therapy. 2. End of 4-week wash-out from paltusotine at end of Evolve/Edge studies.
* Higher score indicates increased symptom burden. ** Components include headache, joint pain, sweating, fatigue, weakness, swelling, and numbness/tingling. The recall period for each questionnaire was 24 h

Clinical Metrics Important to Acromegaly Outcomes Remained Stable Over Time





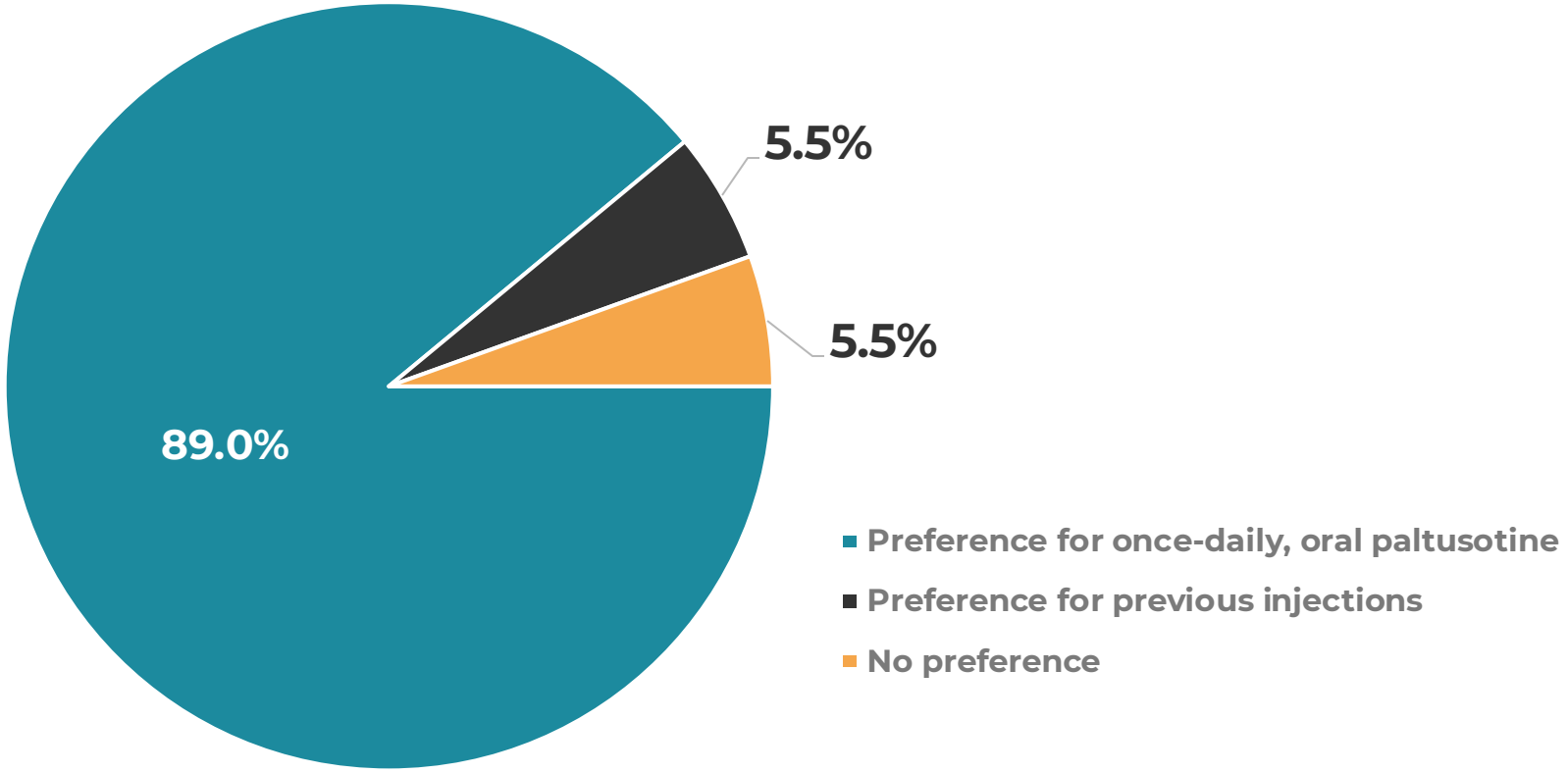




1. Baseline (screening) from Evolve/Edge studies while on injected SRL therapy. 2. End of 4-week wash-out from paltusotine at end of Evolve/Edge studies.
UT: Untreated

Treatment Preference

- At 52 weeks in the study (or at the last visit for those who discontinued the study), participants were asked to choose their preferred treatment option



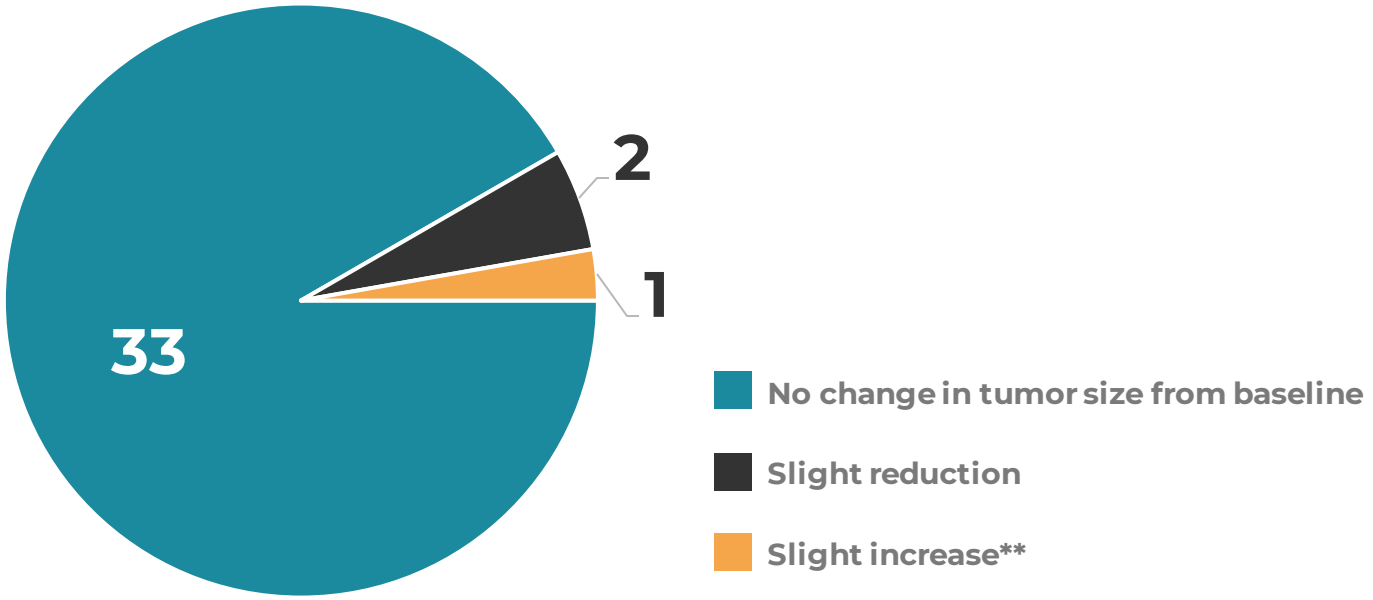
Safety Summary

Treatment-emergent Adverse Events (TEAEs) Occurring in ≥3 Subjects

TEAEs	Any Dose N=43 n (%) m
Headache	13 (30.2) 20
Arthralgia	11 (25.6) 22
Fatigue	8 (18.6) 13
Corona virus infection	7 (16.3) 7
Diarrhea	5 (11.6) 5
Hyperhidrosis	5 (11.6) 7
Myalgia	5 (11.6) 6
Paresthesia	5 (11.6) 8
Anxiety	4 (9.3) 5
Dizziness	4 (9.3) 4
Peripheral swelling	4 (9.3) 9
Hypertension	3 (7.0) 3
Hypotension	3 (7.0) 4

- 6 non-treatment related serious AEs occurred in 5 subjects
- 36 subjects had pituitary MRIs

Pituitary MRI Findings*



n = The number of unique subjects per preferred term. m = The number of occurrences for each preferred term. The safety population is comprised of all subjects who received at least one dose in ACROBAT Advance. * Based on local radiology assessment. ** One subject with no visible tumor at baseline was found to have a 5-mm lesion 13 months following the baseline MRI.

Conclusions

- Once daily, oral paltusotine lowered and maintained IGF-1 and GH at levels comparable to prior injected SRL therapy for up to 103 weeks
- Signs and symptoms associated with acromegaly remained stable over time
- Paltusotine was well tolerated, with a safety profile similar to that of injected SRLs
- Most subjects preferred once-daily, oral paltusotine over injected SRLs

Acknowledgements

This presentation is dedicated to the memory of
Marcello Bronstein, MD, PhD

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Full Author Disclosures

- Monica R. Gadelha reports serving as an advisory board member for Crinetics Pharmaceuticals, Inc. (Crinetics), Ipsen, Novo Nordisk, and Recordati Rare Diseases; as a research investigator for Crinetics and Recordati Rare Diseases; and as a speaker for Ipsen, Novo Nordisk, and Recordati Rare Diseases.
- Harpal Randeva reports no conflicts of interest.
- Murray B. Gordon reports receiving research support from Ascendis, Camurus, Chiasma, Corcept, Crinetics, Ipsen, Novartis, Novo Nordisk, Opko, Pfizer, and Strongbridge; and serving as a scientific consultant for Crinetics, HRA Pharma, Novo Nordisk, and Recordati Rare Diseases.
- Mirjana Doknic reports serving as a research investigator for Crinetics, Pfizer, Camurus, Ascendis, Opko, Ipsen, and Teva; as a speaker for Pfizer, Novartis, Novo Nordisk, Sandoz, and Merck; and as an advisory board member for Pfizer in CEE region.
- Emese Mezősi reports serving as a research investigator for Crinetics.
- Miklós Tóth reports receiving consulting fees from Ipsen, Novartis, Pfizer, and Recordati Rare Diseases; and serving as a research investigator for Crinetics.
- Cesar Luiz Boguszewski reports serving as a research investigator for Crinetics and Recordati Rare Diseases; as a speaker for Ipsen and Recordati Rare Diseases; and as a scientific consultant for Novo Nordisk.
- Christine T. Ferrara-Cook, Alessandra Casagrande, and Alan Krasner are employees of Crinetics.